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Reactions of the Formamidines. XII: Some Derivatives of Desoxybenzoin.

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IN a previous series of papers, (*1*) it has been shown that one of the characteristic properties of compounds containing the acid methylene grouping was their ability to react with disubstituted formamidines, producing a carbon-carbon linking, and yielding an amino-methylene derivative, as follows:

$$\begin{matrix} X \\ \diagdown \\ \quad CH_2 \\ \diagup \\ Y \end{matrix} + RN{:}CH{-}NHR = \begin{matrix} X \\ \diagdown \\ \quad C{:}CH{-}NHR \\ \diagup \\ Y \end{matrix} + RNH_2.$$

Such reactions were found to occur in the case of open-chain compounds such as aceto-acetic ester, benzoyl-acetic ester, cyano-acetic ester, and acetyl-acetone; and also with the heterocyclic thiazolidones, pyrazolones, isoxazolones and imidazolones.

The following work shows that the methylene hydrogen of the grouping C_6H_5-CH_2-CO- in desoxybenzoin (benzyl-phenyl ketone) may be replaced, with difficulty, forming reactive amino-methylene derivatives of the type C_6H_5–CO–C(C_6H_5):CH–NHR. In general, the ease of reaction is determined by the acidity of the methylene grouping; thus compounds containing the complex CO–CH_2–CO substitute the hydrogen of the –CH_2–readily and smoothly. On the other hand, experiments with camphor have failed to yield an amino-methylene derivative.

EXPERIMENTAL.

PREPARATION OF BENZYL-PHENYL KETONE. (*2*.)

Benzoin was heated with zinc dust in glacial acetic acid for twenty-four hours. The reaction mixture was then poured into cold water and the oil which separated extracted with ether. This solu-

tion was then dried with calcium chloride, the ether distilled off, and the residue fractionated under reduced pressure. An average yield of sixty per cent pure desoxybenzoin, boiling at 185-190° at 15 mm. and melting at 55° was thus obtained, a yield decidedly better than afforded by other methods.

ANILIDOMETHYLENE-DESOXYBENZOIN.
PhCOC(Ph):CHNHPh.

A mixture of diphenyl formamidine (24 grams) and desoxybenzoin (24 grams) was heated at 155° in a distilling flask under reduced pressure for two hours. An oil distilled over, which proved to be aniline. The temperature of the bath was then raised to 190° for 15 minutes. The reaction mixture was then treated with dilute acid to remove any unchanged formamidine and then purified by recrystallizations from alcohol.

Analyses: Calculated for $C_{21}H_{17}ON$; N, 4.67%.

Found: 4.63% and 4.55%.

The yellow compound, which melted at 93.5°, is identical with the one obtained by Wislicenus and Ruthing by the action of aniline upon formyl desoxybenzoin, Ph–CO–C(Ph):CHOH. (3.)

p-TOLYL-AMINO-METHYLENE-DESOXYBENZOIN.

This compound, together with p-toluidine, was formed by heating under reduced pressure desoxybenzoin with di-p-tolyl formamidine. The monoclinic crystals from alcohol melted at 132°.

Analyses: Calculated for $C_{22}H_{19}ON$; N, 4.47%.

Found: 4.43% and 4.51%.

p-METHOXY-PHENYL-AMINO-METHYLENE-DESOXYBENZOIN.
$PhCOC(Ph):CH\text{-}NH\text{-}C_6H_4OCH_3$.

Under like conditions at 165°, desoxybenzoin and di-p-anisyl formamidine gave a very poor yield of the above compound, cubical crystals from alcohol, with a melting point of 127°.

Analyses: Calculated for $C_{22}H_{19}O_2N$; N, 4.26%.

Found: 4.31%.

The general reaction involved in all of the above reactions is as follows:

$$Ph\text{–}CO\text{–}C(Ph)H_2 + RN\text{–}CH\text{–}NHR = Ph\text{–}CO\text{–}C(Ph):CHNHR + RNH_2.$$

The yields are unsatisfactory; the best obtained was 14% with di-p-tolyl formamidine, while the results with the di-o-tolyl and

di-p-ethoxyphenyl formamidines were negative. The trouble seems due to the difficulty of finding the optimum temperature of reaction in each case and the case with which deep-seated decomposition products are formed.

REACTIONS OF THE AMINO-METHYLENE DERIVATIVES.

(a) *Acids and Alkalies.*

The p-tolyl compound was unaltered after boiling for four hours with 15% sulphuric acid, or for one hour with 20% sodium hydroxide solution.

(b) *Alcoholic Potash.*

When refluxed for two hours with alcoholic potassium hydroxide solution, the p-tolyl compound was broken down into p-toluidine and benzoic acid.

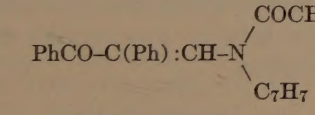
(c) *Acetyl Derivative.* $(C_{22}H_{18}ON)COCH_3$.

The p-tolyl derivative was heated for ten hours with acetic anhydride. The excess of anhydride was decomposed with warm water, and the resulting solid crystallized from hot alcohol. It melted at 111°.

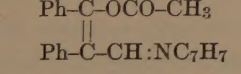
Analyses: Calculated for $C_{24}H_{21}O_2N$; N, 3.94%.

Found: 3.71% and 3.67%.

Warming with dilute potassium hydroxide splits off the acetyl group, yielding the original paratolyl-amino-methylene-desoxybenzoin. Such an acetyl compound could be either a p-tolyl acetamino derivative such as:



Or more probably the acetate of the enol form:



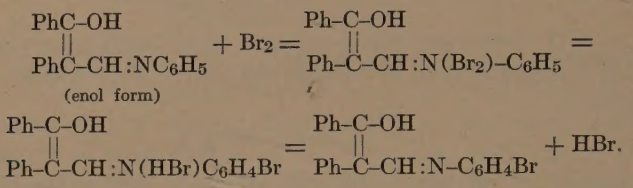
(d) *Action of Bromine upon Anilido-methylene-desoxybenzoin.*

P-Bromo-phenyl-amino-methylene-desoxybenzoin.

One mole of bromine was added to a cooled solution of anilido-methylene-desoxybenzoin in chloroform. One standing, a crystalline yellow compound separated out which melted, with decomposition at 144°. This, when treated with water, lost hydrobromic acid and gave a bromo compound which melted at 167° after recrystallization from alcohol.

Analyses: Calculated for $C_{21}H_{17}ONBr$; N, 3.66%.
Found: N, 3.73% and 3.86%.

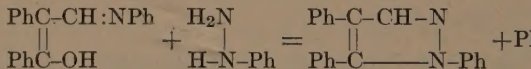
The substance when boiled with alcoholic potash gave benzoic acid and parabromoaniline. This fact, together with the analysis, shows the validity of the above formula. The probable mechanism of the reaction is as follows:



(e) *Synthesis of Ring Compounds.*

1–4–5 Triphenyl Pyrazole.

It was shown in earlier papers that the grouping R–CO–CH: CH–NHR′ will condense in the enol form with hydrazines and yield pyrazoles (*4*). This is true in the present case, since the anilido-methylene compound when boiled with phenyl-hydrazine in alcoholic solution gave the well-known 1-4-5 triphenyl pyrazole (m.p. 212°). (*5.*)



Analyses: Calculated for $C_{21}H_{16}N_2$; N, 9.46%.
Found: 9.41%.

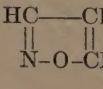
The same pyrazole and paratoluidine were obtained when p-tolyl-amino-methylene-desoxybenzoin was treated under similar conditions with phenyl hydrazine.

4–5 Diphenyl Pyrazole.

The p-tolyl derivative when heated with hydrazine sulphate and potassium carbonate in alcoholic solution combined readily to give p-toluidine and the 4–5 diphenyl pyrazole (m.p. 158°).

Analyses: Calculated for $C_{15}H_{12}N_2$; N, 12.72%.
Found: 12.61% and 12.64%.

Synthesis of 4–5 Diphenyl Isoxazole.



Paratolyl-amino-methylene-desoxybenzoin (ten grams) and hydroxylamine hydrochloride (5 grams) were heated for four hours in a mixture of alcohol (25 cc.) and pyridine (10cc.). On pouring into an excess of cold dilute hydrochloric acid, an oil separated which soon solidified. The filtrate contained p-toluidine and the solid after recrystallization melted at 74.5°.

Analyses: Calculated for $C_{15}H_{11}ON$; N, 6.34%.

Found: 6.18% and 6.44%.

The compound when boiled for a few minutes with 15% sodium hydroxide was hydrolyzed into benzoic acid and small amounts of an oil with the odor of benzyl cyanide. The identity of the compound is proven, then, as 4-5 diphenyl isoxazole, both by its analyses, its decomposition products, and its analogy with the synthesis of other isoxazoles by Dains and Griffith. (*6*.)

SUMMARY.

(1) Certain derivatives of R-amino-methylene desoxybenzoin have been synthesized.

(2) Their behavior with acids, alkalies, acetic anhydride and bromine has been studied.

(3) They have been found to give, with phenyl hydrazine, hydrazine and hydroxylamine, pyrazole and isoxazole ring compounds.

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(3) Ann. 379, 231 (1911).
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(5) Ann. 379, 231 (1911).
(6) Journal Am. Chem. Society 35, 960 (1913).
(7) The authors wish to thank the Research Committee of the University of Kansas for a grant which was of essential aid in this investigation.